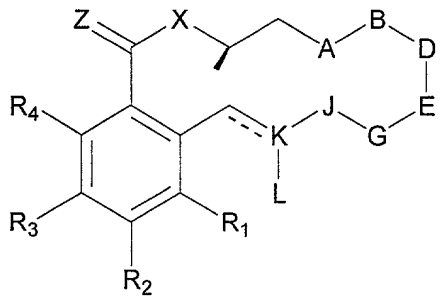
CLAIMS

1. A compound having the structure:



wherein the dotted line --- represents a bond, whereby a double bond is present, or the dotted line --- is absent, whereby a single bond is present;

R_1 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $N(R_A)_2$, wherein each occurrence of R_A is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

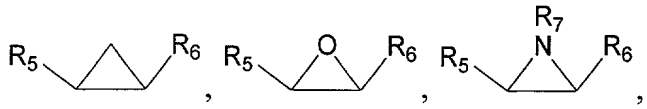
R_2 is hydrogen, halogen, cyano, $-OR_B$, $-N(R_B)_2$, $-SR_B$, $-O(C=O)R_B$, $-N(R_B)(C=O)(R_B)$, $-C(O)R_B$, $-C(O)OR_B$, $-CON(R_B)_2$, $-OCO_2R_B$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_3 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $-N(R_C)_2$, wherein each occurrence of R_C is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_4 is hydrogen, halogen, cyano, $-OR_D$, $-N(R_D)_2$, $-SR_D$, $-O(C=O)R_D$, $-N(R_D)(C=O)(R_D)$, $-C(O)R_D$, $-C(O)OR_D$, $-CON(R_D)_2$, $-OCO_2R_D$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;

A and B together represent  , -CHR_5-CHR_6-, -CR_5=CR_6-, wherein R_5 and R_6 are each independently hydrogen, halogen, cyano, -OR_J, -$N(R_J)_2$, -SR_J, -O(C=O)R_J, -O(S=O)R_J ,-$N(R_J)$(C=O)(R_J), -C(=O)R_J, -C(=O)OR_J, -$CON(R_J)_2$, -OCO_2R_J, -OS(=O)OR_J or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and wherein R_7 is hydrogen, a protecting group, -OR_K, -SR_K, -C(O)OR_K, -C(O)NR_K, -$S(O)_2R_K$, -O(C=O)R_K, -$N(R_K)$(C=O)(R_K), -C(O)R_K, -C(O)OR_K, -$CON(R_K)_2$, -OCO_2R_K, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent -CHR_5-CHR_6-, R_5 and R_6 taken together represent a substituted or unsubstituted 3-7 membered aliphatic, heteroaliphatic, aryl or heteroaryl ring,

D and E together represent -CHR_8-CHR_9-, -CR_8=CR_9-, wherein R_8 and R_9 are each independently hydrogen or lower alkyl;

G and J together represent -CHR_{10}-CHR_{11}-, -CR_{10}=CR_{11}-, wherein R_{10} and R_{11} are each independently hydrogen or lower alkyl;

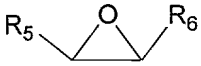
K and L together represent C=O, C=S, CH-CH_3, CH-$CH(R_L)_2$, C=$C(R_L)_2$, -CH_2-, -C(-$S(CH_2)_3$S-)-, CH-OR_L, CH-SR_L, CH-$N(R_L)_2$, CH-$N(R_L)$(C=O)(R_L), C=N-O-R_L, CH-N=O, C=$C(R_L)$-$N(R_L)_2$, C=N-R_L, C=N-$N(R_L)_2$, or, if the dotted line --- represents a bond, whereby a double bond is present, then K and L together represent C-$N(R_L)_2$, wherein each occurrence of R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl, heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;

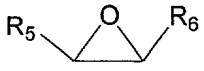
wherein one or any two of R_1, R_A, R_2, R_B, R_3, R_C, R_4, R_D, R_5, R_6, R_J, or R_L are optionally a linker covalently bonded to a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids; and

pharmaceutically acceptable derivatives thereof,

with the proviso that:

(1) if Z is O; if X is O; if A and B together are  and R_5 and R_6 are each hydrogen; if D and E together are –CH=CH-; if G and J together are -CH=CH- ; if K and L together are C=O; if R_1 is hydrogen or Cl; and if R_3 is hydrogen,

then R_2 is not $-OR_B$ or $-O(C=O)R_B$, wherein R_B is hydrogen or an alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, aryl, aryloxy, heterocycle, cycloalkyl, cycloalkenyl, or cycloalkenyl fused to an aryl group; and R_4 is not $-OR_D$ or $-O(C=O)R_D$, wherein R_D is hydrogen or an alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, aryl, aryloxy, heterocycle, cycloalkyl, cycloalkenyl, or cycloalkenyl fused to an aryl group;

(2) if Z is O; if X is O, if R_1 is Cl; if R_2 is OR_A and R_A is hydrogen, alkanoyl, alkenoyl, tert-butyl dimethylsilyl or tert-butyldiphenylsilyl; if R_3 is hydrogen; if R_4 is OR_B and R_B is hydrogen, alkanoyl, alkenoyl, tert-butyldimethylsilyl, or tert-butyldiphenylsilyl; if D and E together are –CH=CH-; if G and J together are -CH=CH-; if A and B together are  or if A and B together are $-CHR_5-CHR_6-$ and R_6 is halogen and R_5 is OR_J, wherein R_J is hydrogen, alkanoyl, or alkenoyl, or R_5 is $-O(S=O)R_J$, wherein R_J is a second compound of formula (I) linked via an oxygen atom present at R_5 in the second compound, and wherein R_6 is halogen; Z is O; X is O, R_1 is Cl; R_2 is OR_A and R_A is hydrogen, alkanoyl, alkenoyl, tert-butyl dimethylsilyl or tert-butyldiphenylsilyl; R_3 is hydrogen; R_4 is OR_B and R_B is hydrogen, alkanoyl, alkenoyl, tert-butyldimethylsilyl, or tert-butyldiphenylsilyl;

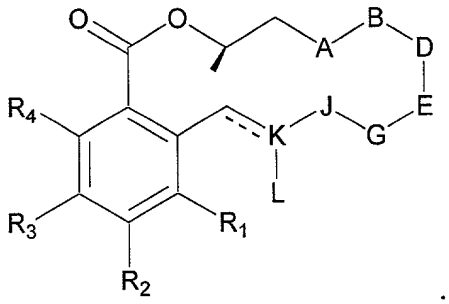
then K and L together are not C=O or C=N-O-R_L, when R_L is hydrogen, or substituted or unsubstituted lower alkyl, a substituted or unsubstituted alkylene moiety, a substituted carbonyl moiety or a substituted or unsubstituted aryl moiety;

except that K and L together can be C=N-O-R_L, when R_L is a linker covalently bonded to a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids; or

2. The method of claim 1, wherein one or any two of R_1, R_A, R_2, R_B, R_3, R_C, R_4, R_D, R_5, R_6, R_J, or R_L are a linker covalently bonded to a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids, wherein the linker is an aliphatic or heteroaliphatic moiety, whereby said aliphatic or heteroaliphatic moiety is substituted or unsubstituted, branched or unbranched, or cyclic or acyclic.

3. The method of claim 1, wherein one or any two of R_1, R_A, R_2, R_B, R_3, R_C, R_4, R_D, R_5, R_6, R_J, or R_L are a linker covalently bonded to a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids, wherein the linker is a moiety having one of the structures -$(CH_2)_n$-CH=CH-$(CH_2)_m$-, -$(CH_2)_p$-C≡C-$(CH_2)_q$-, or -$CH_2(CH_2)_sCH_2$-, wherein each occurrence of n, m, p, q and s is independently an integer from 0-10, and wherein one or more of the hydrogen atoms are optionally replaced with an alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl or alkylheteroaryl moiety or a secondary or tertiary amine, hydroxyl, or thiol.

4. The compound of claim 1, wherein Z and X are each O, and the compound has the structure:



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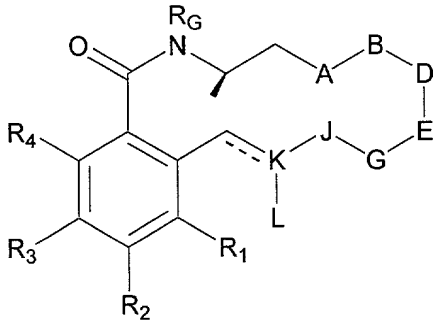
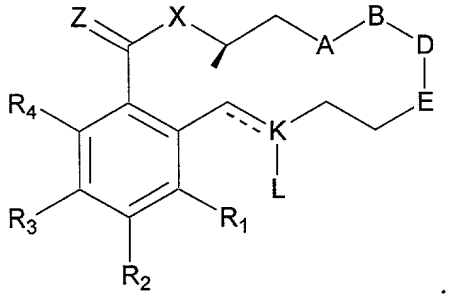
5. The compound of claim 1, wherein Z is O and X is NR_G, and the compound has the structure:



6. The compound of claim 5, wherein R_G is H.

7. The compound of claim 1, wherein G and J together represent $-CH_2-CH_2-$ and the compound has the structure:



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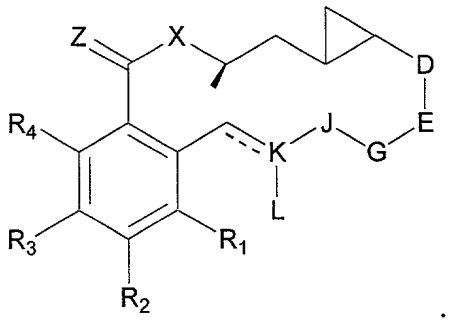
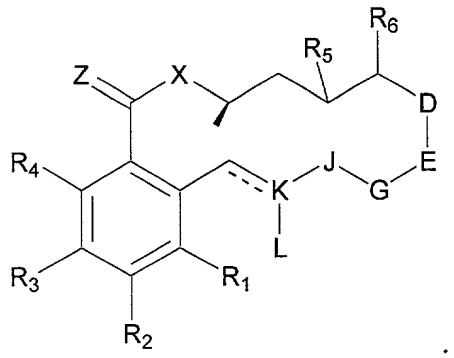
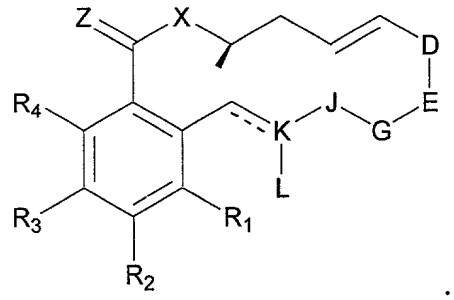
8. The compound of claim 1, wherein A-B is a cyclopropyl ring and the compound has the structure:



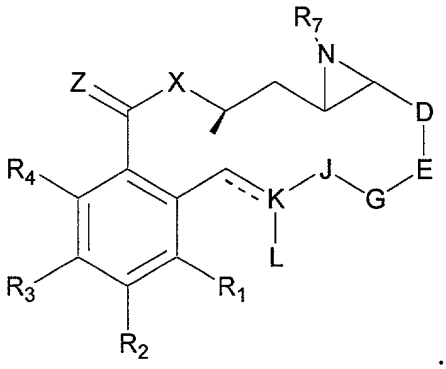
9. The compound of claim 1, wherein A and B together represent -CHR_5-CHR_6- and the compound has the structure:



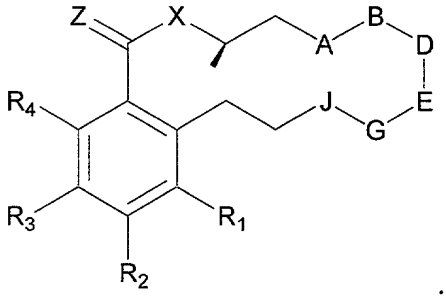
10. The compound of claim 1, wherein A and B together represent -CH=CH- and the compound has the structure:



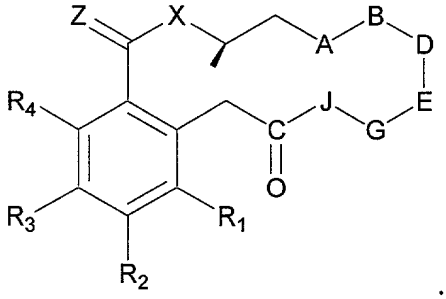
11. The compound of claim 1, wherein A and B together represent an aziridine and the compound has the structure:



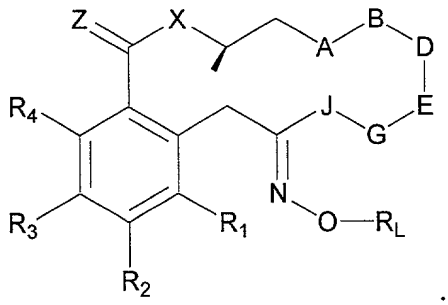
12. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is present, K and L together represent -CH_2- and the compound has the structure:



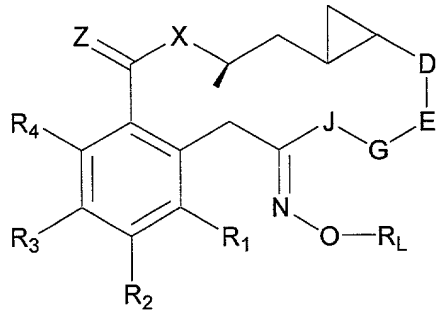
13. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is present, K-L together represent C=O and the compound has the structure:



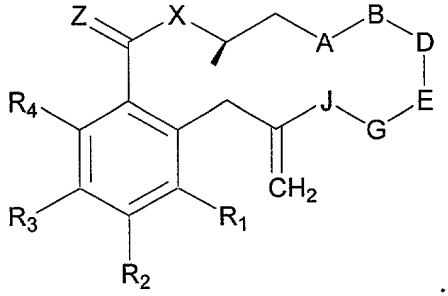
14. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is present, K and L together represent C=N-O-R_L and the compound has the structure:



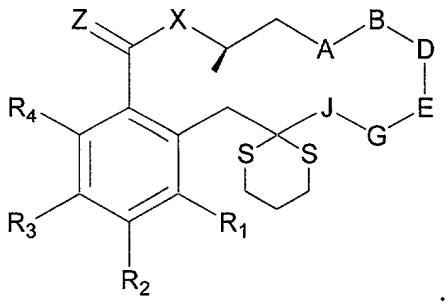
15. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is present, A and B together represent a cyclopropyl group, K and L together represent C=N-O-R_L and the compound has the structure:



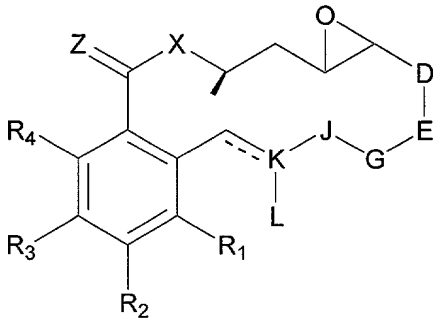
16. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is present, K and L together represent C=CH_2 and the compound has the structure:



17. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is present, K and L together represent a dithiane, -C(-S(CH_2)$_3$S-)-, and the compound has the structure:



18. The compound of claim 1, wherein A and B together represent an epoxide and the compound has the structure:



wherein if Z is O and X is O, then at least one of the D-E, G-J, K-L, R_2 and R_4 are defined as:

R_2 is hydrogen, halogen, cyano, $-N(R_B)_2$, $-SR_B$, $-N(R_B)(C=O)(R_B)$; $-C(O)R_B$, $-C(O)OR_B$, $-CON(R_B)_2$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_3 is not hydrogen;

R_4 is hydrogen, halogen, cyano, $-N(R_D)_2$, $-SR_D$, $-N(R_D)(C=O)(R_D)$, $-C(O)R_D$, $-C(O)OR_D$, $-CON(R_D)_2$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

D and E together represent $-CHR_8-CHR_9-$ wherein R_8 and R_9 are each independently hydrogen or lower alkyl;

G and J together represent $-CHR_{10}-CHR_{11}-$, wherein R_{10} and R_{11} are each independently hydrogen or lower alkyl;

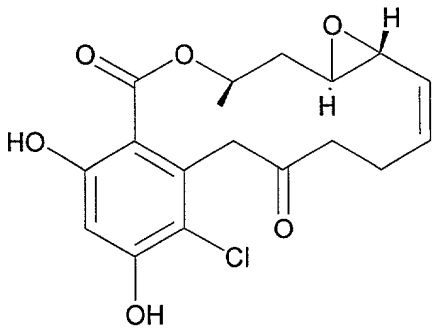
K and L together represent C=S, CH-CH_3, CH-$CH(R_L)_2$, $C=C(R_L)_2$, -CH_2-, -$C(-S(CH_2)_3S-)$-, CH-OR_L, CH-SR_L, CH-$N(R_L)_2$, CH-$N(R_L)(C=O)(R_L)$, CH-N=O, $C=C(R_L)$-$N(R_L)_2$, C=N-R_L, C=N-$N(R_L)_2$, or, if the dotted line --- represents a bond, whereby a double bond is present, then K and L together represent C-$N(R_L)_2$, wherein each occurrence of R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety; or any two of R_1, R_A, R_2, R_B, R_3, R_C, R_4, R_D, R_5, R_6, R_J, or R_L are a linker covalently bonded to a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids.

19. The compound of claim 1, wherein A and B together are -CHR_5-CHR_6- or -CR_5=CR_6- and R_5 and R_6 are each independently hydrogen, halogen, cyano, -OR_J, -$N(R_J)_2$, -SR_J, -O(C=O)R_J, O(S=O)R_J ,-$N(R_J)(C=O)(R_J)$, -OCO_2R_J or -OSO_2R_J and each occurrence of R_J is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety.

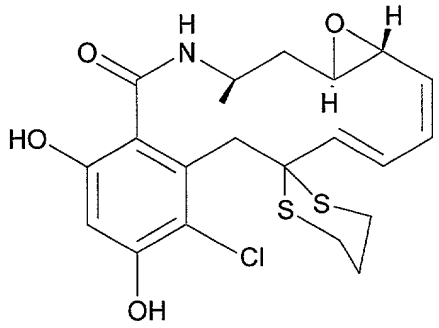
20. The compound of claim 19, wherein R_5 and R_6 are each independently hydrogen, or lower alkyl.

21. The compound of claim 1, wherein R_1 and R_3 are each independently halogen, hydrogen, or lower alkyl; R_2 is hydrogen or -OR_B, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and R_4 is hydrogen or -OR_D, wherein each occurrence of R_D is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety.

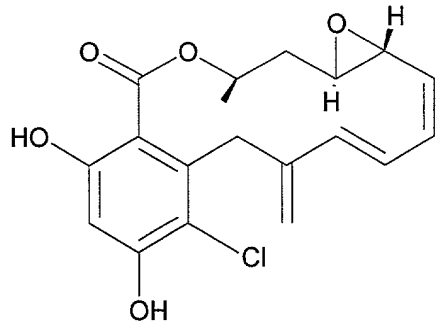
22. The compound of claim 1, wherein the compound has the structure:



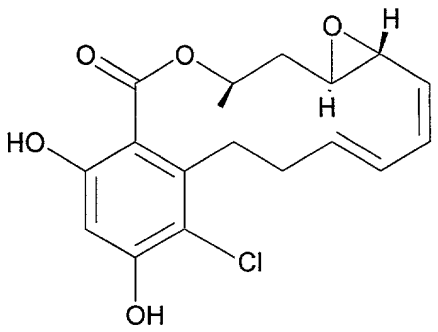
23. The compound of claim 1, wherein the compound has the structure:



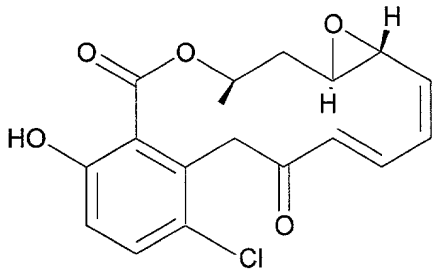
24. The compound of claim 1, wherein the compound has the structure:



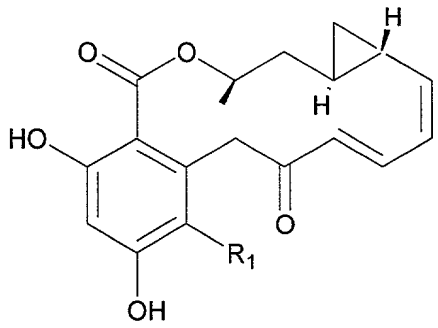
25. The compound of claim 1, wherein the compound has the structure:



26. The compound of claim 1, wherein the compound has the structure:

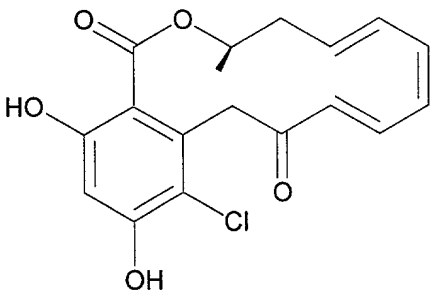


27. The compound of claim 1, wherein the compound has the structure:

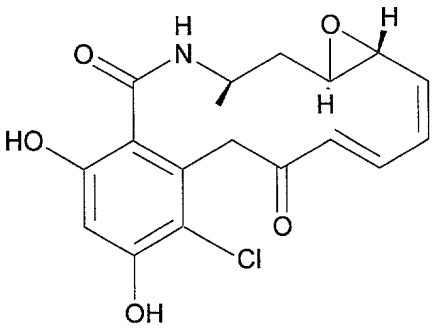


wherein R_1 is hydrogen or Cl.

28. The compound of claim 1, wherein the compound has the structure:



29. The compound of claim 1, wherein the compound has the structure:



30. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

31. The pharmaceutical composition of claim 30, further comprising one or more additional therapeutic agents.

32. The pharmaceutical composition of claim 31, wherein the one or more additional therapeutic agents comprises an anticancer agent.

33. A method for treating cancer comprising:

administering a therapeutically effective amount of a compound of claim 1 to a subject in need thereof.

34. The method of claim 33, wherein the therapeutically effective amount is in the range of 0.001 mg/kg to 50 mg/kg of body weight.

35. The method of claim 33, wherein the therapeutically effective amount is in the range of 0.01 mg/kg to about 25 mg/kg of body weight.

36. The method of claim 33, said method further comprising administering one or more additional therapeutic agents in combination with the compound.

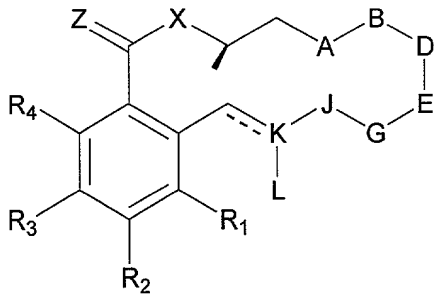
37. The method of claim 36, wherein the one or more additional therapeutic agents comprises an anticancer agent.

38. A method for inhibiting the growth of or killing cancer cells, said method comprising:

contacting the cancer cells with an amount of a compound of claim 1 effective to inhibit the growth of or kill cancer cells.

39. A method for treating a cancer in which the cancer cells comprise Rb negative cancer cells, said method comprising:

administering a therapeutically effective amount of a compound to a subject in need thereof, which therapeutically effective amount is sufficient to inhibit the growth of or kill Rb negative cancer cells, which compound has the structure:



wherein the dotted line --- represents a bond, whereby a double bond is present, or the dotted line --- is absent, whereby a single bond is present;

R_1 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $N(R_A)_2$, wherein each occurrence of R_A is independently hydrogen, a

protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

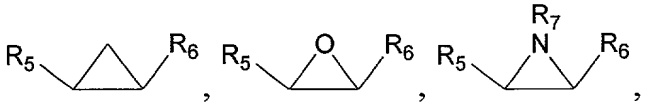
R_2 is hydrogen, halogen, cyano, $-OR_B$, $-N(R_B)_2$, $-SR_B$, $-O(C=O)R_B$, $-N(R_B)(C=O)(R_B)$, $-C(O)R_B$, $-C(O)OR_B$, $-CON(R_B)_2$, $-OCO_2R_B$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_3 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $-N(R_C)_2$, wherein each occurrence of R_C is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_4 is hydrogen, halogen, cyano, $-OR_D$, $-N(R_D)_2$, $-SR_D$, $-O(C=O)R_D$, $-N(R_D)(C=O)(R_D)$, $-C(O)R_D$, $-C(O)OR_D$, $-CON(R_D)_2$, $-OCO_2R_D$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;

A and B together represent  , $-CHR_5-CHR_6-$, $-CR_5=CR_6-$, wherein R_5 and R_6 are each independently hydrogen, halogen, cyano, $-OR_J$, $-N(R_J)_2$, $-SR_J$, $-O(C=O)R_J$, $-O(S=O)R_J$,$-N(R_J)(C=O)(R_J)$, $-C(=O)R_J$, $-C(=O)OR_J$, $-CON(R_J)_2$, $-OCO_2R_J$, $-OS(=O)OR_J$ or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and wherein R_7 is hydrogen, a protecting group, $-OR_K$, $-SR_K$, $-C(O)OR_K$, $-C(O)NR_K$, $-S(O)_2R_K$, $-O(C=O)R_K$, $-N(R_K)(C=O)(R_K)$, $-C(O)R_K$, $-C(O)OR_K$, $-CON(R_K)_2$, $-OCO_2R_K$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence

of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent -CHR_5-CHR_6-, R_5 and R_6 taken together represent a substituted or unsubstituted 3-7 membered aliphatic, heteroaliphatic, aryl or heteroaryl ring,

D and E together represent -CHR_8-CHR_9-, -CR_8=CR_9-, wherein R_8 and R_9 are each independently hydrogen or lower alkyl;

G and J together represent -CHR_{10}-CHR_{11}-, -CR_{10}=CR_{11}-, wherein R_{10} and R_{11} are each independently hydrogen or lower alkyl;

K and L together represent C=O, C=S, CH-CH_3, CH-$CH(R_L)_2$, C=$C(R_L)_2$, -CH_2-, -C(-$S(CH_2)_3S$-)-, CH-OR_L, CH-SR_L, CH-$N(R_L)_2$, CH-$N(R_L)(C=O)(R_L)$, C=N-O-R_L, CH-N=O, C=$C(R_L)$-$N(R_L)_2$, C=N-R_L, C=N-$N(R_L)_2$, or, if the dotted line --- represents a bond, whereby a double bond is present, then K and L together represent C-$N(R_L)_2$, wherein each occurrence of R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl, heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;

wherein one or any two of R_1, R_A, R_2, R_B, R_3, R_C, R_4, R_D, R_5, R_6, R_J, or R_L are optionally a linker covalently bonded to a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids; and

pharmaceutically acceptable derivatives thereof.

40. The method of claim 39, wherein the therapeutically effective amount is in the range of 0.001 mg/kg to 50 mg/kg of body weight.

41. The method of claim 39, wherein the therapeutically effective amount is in the range of 0.01 mg/kg to about 25 mg/kg of body weight.

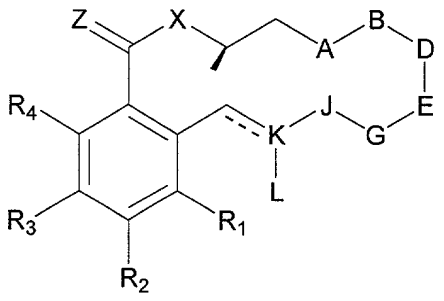
42. The method of claim 39, said method further comprising administering one or more additional therapeutic agents in combination with the compound.

43. The method of claim 42, wherein the one or more additional therapeutic agents comprises a anticancer agent

44. The method of claim 39, wherein the cancer comprising Rb negative cells is small cell lung cancer, glioblastoma or retinoblastoma.

45. A method for inhibiting the growth of or killing Rb negative cancer cells, said method comprising:

contacting the cells with an amount of a compound effective to inhibit the growth of or kill Rb negative cancer cells, which compound has the structure:



wherein the dotted line --- represents a bond, whereby a double bond is present, or the dotted line --- is absent, whereby a single bond is present;

R_1 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $N(R_A)_2$, wherein each occurrence of R_A is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

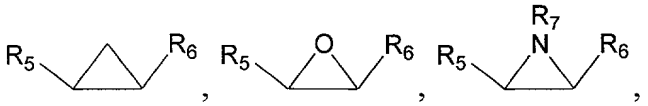
R_2 is hydrogen, halogen, cyano, $-OR_B$, $-N(R_B)_2$, $-SR_B$, $-O(C=O)R_B$, $-N(R_B)(C=O)(R_B)$, $-C(O)R_B$, $-C(O)OR_B$, $-CON(R_B)_2$, $-OCO_2R_B$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_3 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $-N(R_C)_2$, wherein each occurrence of R_C is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_4 is hydrogen, halogen, cyano, $-OR_D$, $-N(R_D)_2$, $-SR_D$, $-O(C=O)R_D$, $-N(R_D)(C=O)(R_D)$, $-C(O)R_D$, $-C(O)OR_D$, $-CON(R_D)_2$, $-OCO_2R_D$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;

A and B together represent 

$-CHR_5-CHR_6-$, $-CR_5=CR_6-$, wherein R_5 and R_6 are each independently hydrogen, halogen, cyano, $-OR_J$, $-N(R_J)_2$, $-SR_J$, $-O(C=O)R_J$, $-O(S=O)R_J$,$-N(R_J)(C=O)(R_J)$, $-C(=O)R_J$, $-C(=O)OR_J$, $-CON(R_J)_2$, $-OCO_2R_J$, $-OS(=O)OR_J$ or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and wherein R_7 is hydrogen, a protecting group, $-OR_K$, $-SR_K$, $-C(O)OR_K$, $-C(O)NR_K$, $-S(O)_2R_K$, $-O(C=O)R_K$, $-N(R_K)(C=O)(R_K)$, $-C(O)R_K$, $-C(O)OR_K$, $-CON(R_K)_2$, $-OCO_2R_K$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent $-CHR_5-CHR_6-$, R_5 and R_6 taken together represent a substituted or unsubstituted 3-7 membered aliphatic, heteroaliphatic, aryl or heteroaryl ring,

D and E together represent $-CHR_8-CHR_9-$, $-CR_8=CR_9-$, wherein R_8 and R_9 are each independently hydrogen or lower alkyl;

G and J together represent -CHR_{10}-CHR_{11}-, -CR_{10}=CR_{11}-, wherein R_{10} and R_{11} are each independently hydrogen or lower alkyl;

K and L together represent C=O, C=S, CH-CH_3, CH-$CH(R_L)_2$, $C=C(R_L)_2$, -CH_2-, -$C(-S(CH_2)_3S-)$-, CH-OR_L, CH-SR_L, CH-$N(R_L)_2$, CH-$N(R_L)(C=O)(R_L)$, C=N-O-R_L, CH-N=O, $C=C(R_L)$-$N(R_L)_2$, C=N-R_L, C=N-$N(R_L)_2$, or, if the dotted line --- represents a bond, whereby a double bond is present, then K and L together represent C-$N(R_L)_2$, wherein each occurrence of R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

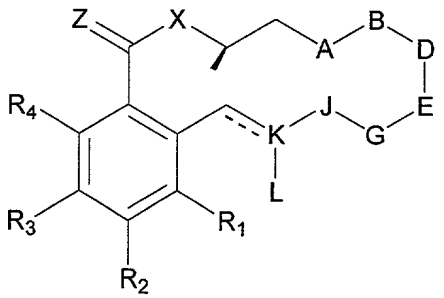
whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl, heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;

wherein one or any two of R_1, R_A, R_2, R_B, R_3, R_C, R_4, R_D, R_5, R_6, R_J, or R_L are optionally a linker covalently bonded to a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids; and

pharmaceutically acceptable derivatives thereof.

46. The method of claim 45, wherien the Rb negative cancer cells are small cell lung cancer, glioblastoma or retinoblastoma cells.

47. A method for the synthesis of a compound having the structure **(I)**:



(I)

wherein the dotted line --- represents a bond, whereby a double bond is present, or the dotted line --- is absent, whereby a single bond is present;

R_1 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $N(R_A)_2$, wherein each occurrence of R_A is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

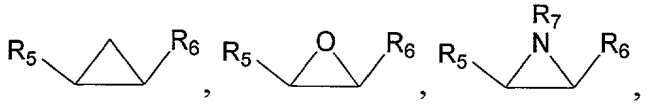
R_2 is hydrogen, halogen, cyano, $-OR_B$, $-N(R_B)_2$, $-SR_B$, $-O(C=O)R_B$, $-N(R_B)(C=O)(R_B)$, $-C(O)R_B$, $-C(O)OR_B$, $-CON(R_B)_2$, $-OCO_2R_B$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_3 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $-N(R_C)_2$, wherein each occurrence of R_C is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_4 is hydrogen, halogen, cyano, $-OR_D$, $-N(R_D)_2$, $-SR_D$, $-O(C=O)R_D$, $-N(R_D)(C=O)(R_D)$, $-C(O)R_D$, $-C(O)OR_D$, $-CON(R_D)_2$, $-OCO_2R_D$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;

A and B together represent 

, , ,

$-CHR_5-CHR_6-$, $-CR_5=CR_6-$, wherein R_5 and R_6 are each independently hydrogen, halogen, cyano, $-OR_J$, $-N(R_J)_2$, $-SR_J$, $-O(C=O)R_J$, $-O(S=O)R_J$,$-N(R_J)(C=O)(R_J)$, $-C(=O)R_J$, $-C(=O)OR_J$, $-CON(R_J)_2$, $-OCO_2R_J$, $-OS(=O)OR_J$ or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting

group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and wherein R_7 is hydrogen, a protecting group, $-OR_K$, $-SR_K$, $-C(O)OR_K$, $-C(O)NR_K$, $-S(O)_2R_K$, $-O(C=O)R_K$, $-N(R_K)(C=O)(R_K)$, $-C(O)R_K$, $-C(O)OR_K$, $-CON(R_K)_2$, $-OCO_2R_K$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent $-CHR_5-CHR_6-$, R_5 and R_6 taken together represent a substituted or unsubstituted 3-7 membered aliphatic, heteroaliphatic, aryl or heteroaryl ring,

D and E together represent $-CHR_8-CHR_9-$, $-CR_8=CR_9-$, wherein R_8 and R_9 are each independently hydrogen or lower alkyl;

G and J together represent $-CHR_{10}-CHR_{11}-$, $-CR_{10}=CR_{11}-$, wherein R_{10} and R_{11} are each independently hydrogen or lower alkyl;

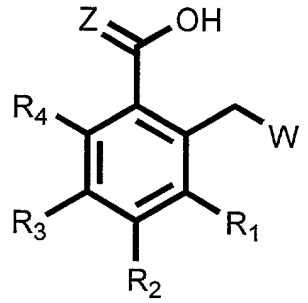
K and L together represent C=O, C=S, CH-CH_3, CH-$CH(R_L)_2$, C=$C(R_L)_2$, $-CH_2-$, $-C(-S(CH_2)_3S-)-$, CH-OR_L, CH-SR_L, CH-$N(R_L)_2$, CH-$N(R_L)(C=O)(R_L)$, C=N-O-R_L, CH-N=O, C=$C(R_L)$-$N(R_L)_2$, C=N-R_L, C=N-$N(R_L)_2$, or, if the dotted line --- represents a bond, whereby a double bond is present, then K and L together represent C-$N(R_L)_2$, wherein each occurrence of R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl, heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;

wherein one or any two of R_1, R_A, R_2, R_B, R_3, R_C, R_4, R_D, R_5, R_6, R_J, or R_L are optionally a linker covalently bonded to a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids;

said method comprising:

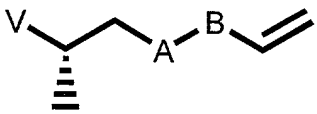
(1) providing a benzoic acid component having the structure:



II

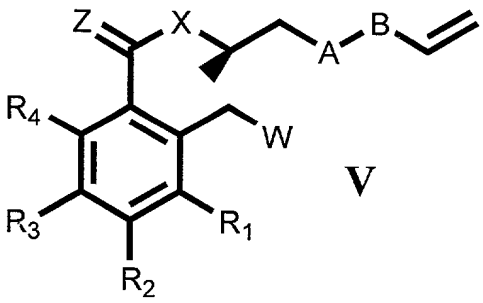
wherein R_1-R_4 and Z are as defined above, and wherein W is halogen; and

reacting the benzoic acid component with a chiral component (**IV**) having the structure:



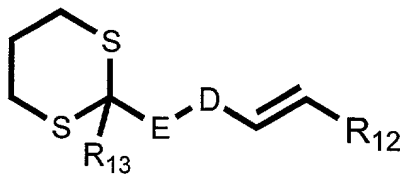
IV

wherein A and B are as defined above, and wherein V is NHR_G, wherein R_G is hydrogen or lower alkyl; SH; or OH in the presence of an esterification reagent to generate an intermediate (**V**) having the structure:



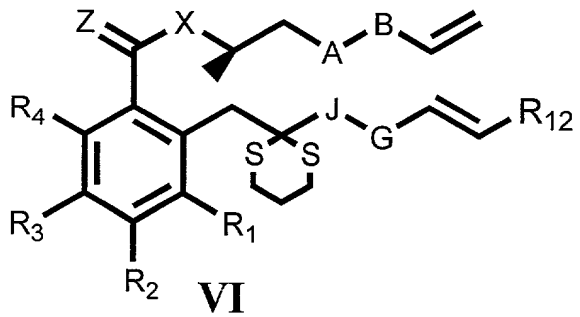
V

(2) reacting the intermediate (**V**) with a dithiane having the structure (**III**):



III

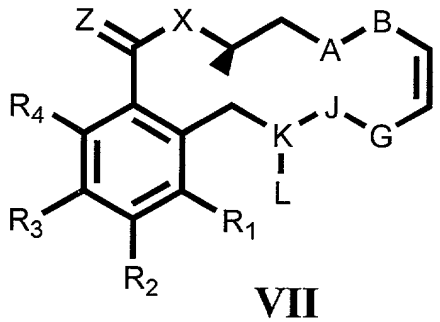
wherein R_{13} is hydrogen or an alkali metal salt and wherein R_{12} is hydrogen or lower alkyl under conditions to add the dithiane to generate an intermediate (**VI**) having the structure:



VI

(3) if any one or more of R_1-R_4 is an unprotected thio, amino or hydroxyl group, optionally protecting said unprotected group;

(4) cyclizing the compound in the presence of an olefin metathesis catalyst to generate the compound (**VII**):



VII

(5) optionally further reacting (**VII**) with one or more reagents to diversify and optionally deprotecting the macrolide to generate the compound (**I**).

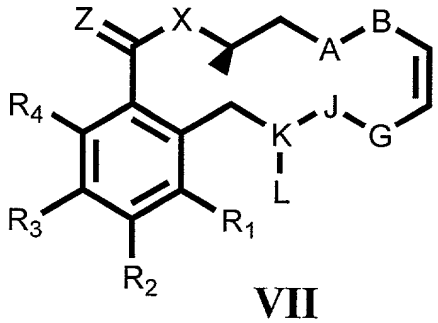
48. The method of claim 47, wherein the step of esterification is performed using diethylazodicarboxylate (DIAD) in the presence of triphenylphosphine or trifurylphosphine.

49. The method of claim 47, wherein the step of olefin metathesis is performed using an olefin metathesis catalyst.

50. The method of claim 47, wherein the step of olefin metathesis is performed using a ruthenium-based olefin metathesis catalyst.

51. The method of claim 50, wherein the step of olefin metathesis is performed using Ru(1,3-dimesityl-4,5-dihydro-imidazol-2-ylidene)(=CHCH=$C(CH_3)_2$)PCp_3Cl_2.

52. A method for synthesis of a macrocycle having the structure **(VII):**



VII

wherein the dotted line --- represents a bond, whereby a double bond is present, or the dotted line --- is absent, whereby a single bond is present;

R_1 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $N(R_A)_2$, wherein each occurrence of R_A is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_2 is hydrogen, halogen, cyano, $-OR_B$, $-N(R_B)_2$, $-SR_B$, $-O(C=O)R_B$, $-N(R_B)(C=O)(R_B)$, $-C(O)R_B$, $-C(O)OR_B$, $-CON(R_B)_2$, $-OCO_2R_B$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

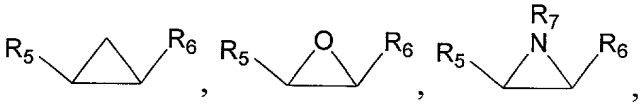
R_3 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or $-N(R_C)_2$, wherein each occurrence of R_C is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R_4 is hydrogen, halogen, cyano, $-OR_D$, $-N(R_D)_2$, $-SR_D$, $-O(C=O)R_D$, $-N(R_D)(C=O)(R_D)$,

$-C(O)R_D$, $-C(O)OR_D$, $-CON(R_D)_2$, $-OCO_2R_D$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;

A and B together represent 

$-CHR_5-CHR_6-$, $-CR_5=CR_6-$, wherein R_5 and R_6 are each independently hydrogen, halogen, cyano, $-OR_J$, $-N(R_J)_2$, $-SR_J$, $-O(C=O)R_J$, $-O(S=O)R_J$,$-N(R_J)(C=O)(R_J)$, $-C(=O)R_J$, $-C(=O)OR_J$, $-CON(R_J)_2$, $-OCO_2R_J$, $-OS(=O)OR_J$ or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and wherein R_7 is hydrogen, a protecting group, $-OR_K$, $-SR_K$, $-C(O)OR_K$, $-C(O)NR_K$, $-S(O)_2R_K$, $-O(C=O)R_K$, $-N(R_K)(C=O)(R_K)$, $-C(O)R_K$, $-C(O)OR_K$, $-CON(R_K)_2$, $-OCO_2R_K$, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent $-CHR_5-CHR_6-$, R_5 and R_6 taken together represent a substituted or unsubstituted 3-7 membered aliphatic, heteroaliphatic, aryl or heteroaryl ring,

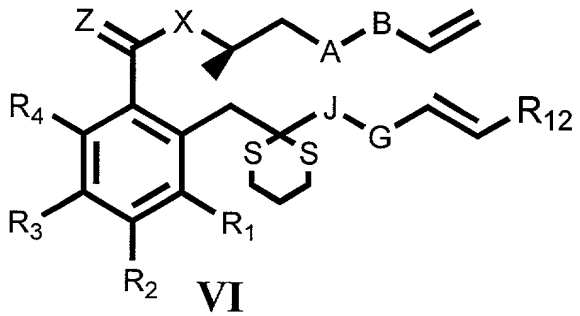
G and J together represent $-CHR_{10}-CHR_{11}-$, $-CR_{10}=CR_{11}-$, wherein R_{10} and R_{11} are each independently hydrogen or lower alkyl;

K and L together represent C=O, C=S, $CH-CH_3$, $CH-CH(R_L)_2$, $C=C(R_L)_2$, $-CH_2-$, $-C(-S(CH_2)_3S-)-$, $CH-OR_L$, $CH-SR_L$, $CH-N(R_L)_2$, $CH-N(R_L)(C=O)(R_L)$, $C=N-O-R_L$, CH-N=O, $C=C(R_L)-N(R_L)_2$, $C=N-R_L$, $C=N-N(R_L)_2$, or, if the dotted line --- represents a bond, whereby a double bond is present, then K and L together represent $C-N(R_L)_2$, wherein each occurrence of R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl,

alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl, heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;

wherein said method comprises cyclizing the intermediate (**VI**):



VI

wherein R_{12} is hydrogen or lower alkyl, in the presence of an olefin metathesis catalyst to generate the compound (**VII**).

53. The method of claim 52, wherein the method further comprises further diversifying the compound (**VII**) to generate a compound having the structure (**I**) as defined herein.

54. The method of claim 52, wherein the step of olefin metathesis is performed using an olefin metathesis catalyst.

55. The method of claim 52, wherein the step of olefin metathesis is performed using a ruthenium-based olefin metathesis catalyst.

56. The method of claim 55, wherein the step of olefin metathesis is performed using Ru(1,3-dimesityl-4,5-dihydro-imidazol-2-ylidene)(=CHCH=$C(CH_3)_2$)PCp_3Cl_2.